REMARKS

I. Status of the Claims

Claims 1 and 19-34 are pending in the application, and claim 1 stands withdrawn. Claims 19-34 are thus under examination and stand rejected, variously, under 35 U.S.C. §112 (second paragraph), §102 and §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Objections

Following the provisional election communicated by telephone, applicants affirm that the claims will be restricted to the following 10 sequences: SEQ ID NOs: 4, 14, 35, 44, 49, 50, 59, 60, 71 and 72. However, there is one correction to be made regarding SEQ ID NO 35 (PBGD_RT15b). SEQ ID NO 35 as given in the present sequence listing, in the present claims and in amended Table 6 contains the following error at the underlined nucleotide positions: TGG GGC CCT **GC**T GGA ATG. The correct sequence of SEQ ID NO 35 (PBGD_RT15b), as given in the description of US2006/0147928 on page 4, table of paragraph [0021], and in Table 6 of Example 3 as originally filed, is TGG GGC CCT **CG**T GGA ATG.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 22, 23, 28-32 and 34 stand rejected as indefinite. Claim 34 has been canceled, rendering the rejection moot. Claims 19 and 27 have been amended, and thus it is believed that claims 22-23, 28-32 are no longer indefinite because the subject matter therein is now clearly defined by hybridization of the at least one cDNA-primer to transcripts of the functional genes of MAGE subfamilies A, B and/or C (Claim 22) or of MAGE-A 1, 2, 3, 4, 6, 10 and/or 12 (Claim

23), or by hybridization of a further cDNA-primer to the mRNA of porphobilinogen desaminase (PBGD), glyceraldehyde-3-phosphat dehydrogenase (GAPDH), β-2-microglobulin or β-actin (claim 28 and dependent claims 29-32). Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejections Under 35 U.S.C. §102

Claims 19, 22, 23, 27 and 28 are not anticipated by U.S. Patent 5,386,022. It is disclosed in the description of the present invention (US2006/0147928, page 2, lanes 29-33 of paragraph [0011]) that, for reverse transcription, the at least one suitable cDNA-primer is required to hybridize to the mRNA (*i.e.*, transcript) of one ***or more*** different members of the MAGE gene family. Therefore, the equivalent property of the substance matter making it suitable for reverse transcription of at least two different MAGE gene transcripts is now included in amended claim 19. In addition, claim 27 is amended with regard to the reverse transcription of an appropriate calibrator mRNA. As a consequence the '022 patent, relating to primers hybridizing to RNAs of AIDS viruses, fails to teach each element of amended claims 19 and 27.

Claims 19, 22 and 23 are not anticipated by U.S. Patent 6,057,105 because the reference relates to ***PCR-primers*** (SEQ ID NO: 1, 2, 23, 24) for amplification, and not to ***cDNA-primers*** for reverse transcription as the present invention (US2006/0147928). The '105 patent teaches using at least one primer for simultaneous ***amplification*** of at least two different MAGE templates in a single ***polymerase chain reaction (PCR)***. In contrast, the present invention teaches using at least one cDNA-primer for simultaneous ***reverse transcription*** of at least two different MAGE transcripts in a single ***cDNA-synthesis reaction***. Actually, the '105 patent teaches carrying out cDNA-synthesis by reverse transcription using unspecific priming by

oligo(dT) (U.S. Patent 6,057,105, Example XIII, referring to Example X, column 27, lines 35-38) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention.

Likewise, the '105 patent teaches ***PCR-amplification*** of β-actin (and suitable PCR-primers therefor) along with PCR-amplification of MAGE from cDNA synthesized by unspecific reverse transcription using oligo(dT). In contrast, the present invention teaches cDNA-primers hybridizing to at least two different MAGE gene transcripts and to an appropriate calibrator mRNA like that of beta-actin, respectively, for simultaneous ***reverse transcription*** of MAGE and calibrator mRNA in a single cDNA-synthesis reaction. Therefore, claims 27 and 28 also are not anticipated by the '105 patent.

Claims 19, 22 and 23 are not anticipated by Kirken *et al.* (US2006/0051324) because Kirken *et al.* (like the '105 patent) relates to ***PCR-primers*** (Table 2, page 11 [0144]) for amplification of MAGE-A1, 3, 4, 6, 10, 12 and not to ***cDNA-primers*** for reverse transcription as the present invention. Kirken *et al.* teach using at least one primer for simultaneous ***amplification*** of at least two different MAGE templates in a single ***polymerase chain reaction (PCR)***. In contrast, the present invention teaches using at least one cDNA-primer for simultaneous ***reverse transcription*** of at least two different MAGE transcripts in a single ***cDNA-synthesis reaction***. Actually, Kirken *et al.* (again, like the '105 patent) teach carrying out cDNA-synthesis by reverse transcription using unspecific priming by oligo(dT) (US2006/0051324, Example I, page 10 [0144], lanes 18-20) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention.

Likewise, Kirken *et al.* teach ***PCR-amplification*** of GAPDH (and suitable PCR-primers therefor) along with PCR-amplification of MAGE from cDNA synthesized by unspecific reverse

transcription using oligo(dT). In contrast, the present invention teaches cDNA-primers hybridizing to at least two different MAGE gene transcripts and to an appropriate calibrator mRNA like that of GAPDH, respectively, for simultaneous ***reverse transcription*** of MAGE and calibrator mRNA in a single cDNA-synthesis reaction. Therefore, claims 27 and 28 also are not anticipated by Kirken *et al.*

Reconsideration and withdrawal of each of the preceding rejections is therefore respectfully requested.

V. Rejections Under 35 U.S.C. §103

A. Kirken *et al.*

Claims 20, 21 and 24 stand rejected as obvious over Kirken *et al.* As discussed above, this reference relates to ***PCR-primers*** (Table 2, page 11 [0144]) for amplification of MAGE-A1, 3, 4, 6, 10, 12 and not to ***cDNA-primers*** for reverse transcription as the present invention (US 2006/0147928). Therefore, ***PCR-primer*** MAGE-A1 Anti-sense by Kirken *et al.* (Table 2, page 11 [0144]), which differs from SEQ ID NO: 14 of the present invention by 3 nucleotides, does not anticipate SEQ ID NO: 14 (Mg1_RT5a) as ***cDNA-primer***. For example, U.S. Patent 6,537,777 by Gellerfors *et al.* teach the PCR-primer Ico381 (SEQ ID NO: 18) for amplification of PBGD (column 11, 13 and Table 1). However, the oligonucleotide PBGD_RT1 (SEQ ID NO: 76 of the present invention US2006/0147928) although essentially overlaping in sequence with PCR-primer Ico381 as taught by Gellerfors *et al.* totally failed to work as cDNA-primer in a reverse transcription reaction (Example 3 and Table 7 of the present invention US 2006/0147928). This clearly demonstrates, that suitability of an oligonucleotide as PCR-primer is not predictive for its suitability as cDNA-primer. Therefore, the skilled artisan would ***not*** have

had a reasonable expectation of success in making a ***cDNA-primer*** with the same sequence as the ***PCR-primer*** of Kirken *et al.* and shortening it by three nucleotides. Thus, it was by no means obvious to one of ordinary skill in the art at the time of the present invention to make a composition comprising at least one cDNA-primer with the sequence of SEQ ID NO: 14 (Mg1_RT5a). Accordingly, claims 20, 21 and 24 are not anticipated by Kirken *et al.*

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

B. Kirken *et al.* in view of Scanlan *et al.* and Buck *et al.*

Claims 25 and 26 are rejected as obvious over Kirken *et al.* in view of Scanlan *et al.* and Buck *et al.* As pointed out above, Kirken *et al.* relates to ***PCR-primers*** (Table 2, page 11 [0144]) for amplification of MAGE-A1, 3, 4, 6, 10, 12 and not to ***cDNA-primers*** for reverse transcription as the present invention (US2006/0147928). Likewise, U.S. Patent 6,686,147 by Scanlan *et al.* teaches amplification primers such as ***PCR-primers*** for the detection of cancer associated antigen genes (column 14, lanes 5-8) but no ***cDNA-primers*** for reverse transcription as the present invention. Actually, Scanlan *et al.* teach carrying out cDNA-synthesis by reverse transcription using unspecific priming by random hexamers (U.S. Patent 6,686,147, column 36, lanes 41-46) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention. The present invention teaches "that reverse transcription of the different MAGE transcripts and optionally of the calibrator mRNA must be carried out simultaneously in a single cDNA-synthesis reaction, using highly selected oligonucleotide primers and sophisticated reaction conditions for reverse transcription, which could not be anticipated from the prior art" (US2006/0147928, page 2, lanes 2-8 of paragraph [0010]). As demonstrated in Example 2 of the present invention, "neither unspecific reverse transcription using cDNA-

priming with oligo-dT" (as taught by Hoon and Kirken) "or random hexanucleotides" (as taught by Scanlan) "nor specific cDNA-priming with an established combination of mono- and dual-specific oligonucleotides hybridizing to the different MAGE-transcripts, respectively, proved to be sufficient for obtaining specific amplification products at the desired high sensitivity level for each member of the MAGE family selected as marker for the subsequent real-time PCR" (US 2006/0147928, page 2, lanes 14-22 of paragraph [0011]). Because of "frequent interferences among different RT-primers" (*i.e.*, cDNA-primers), the choice of the right oligonucleotides as cDNA-primers to be used in a single cDNA-synthesis reaction was "neither predictable from cDNA-synthesis reactions with only one RT-primer" (*i.e.*, cDNA-primer) "nor from the teachings of the prior art" (US2006/0147928, page 2, lanes 37-40 of paragraph [0011]) including prior art like Hoon *et al.*, Kirken *et al.* and Scanlan *et al.* teaching oligonucleotides different from those of the present invention against members of the same template family (*i.e.*, the MAGE gene family) but for a totally different purpose (amplification versus reverse transcription primers), which makes essentially different demands on the oligonucleotide.

Buck *et al.* (Biotechniques, Sept. 1999, Vol. 27, No. 3, pp. 528-536) exclusively relates to sequencing which is an even more different purpose of oligonucleotides with a particularly high primer exchangeablity, which does not at all apply to the sophisticated requirements of cDNA-primers for reverse transcription within a single cDNA-synthesis reaction for obtaining specific amplification products at the desired high sensitivity level for each member of the MAGE family selcted as marker for the subsequent real-time PCR in the present invention. As demonstrated above by the example of a PBGD-primer, suitablility of an oligonucleotide as PCR-primer is not predictive for its suitability as cDNA-primer. Therefore, the skilled artisan would ***not*** have had a reasonable expectation of success in making ***cDNA-primers*** similar to the

PCR-primers of Kirken *et al.*, Scanlan *et al.* or Hoon *et al.* Thus, it was by no means obvious to one of ordinary skill in the art at the time of the present invention to make a composition comprising at least one cDNA-primer with the sequence of SEQ ID NO: 4 (MgRT3a) and/or SEQ ID NO: 14 (Mg1_RT5a). Accordingly, claims 25-26 are not anticipated by Kirken *et al.*, Scanlan *et al.* and/or Buck *et al.*

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

C. Hoon *et al.*/Kirken *et al.* in view of Gellerfors *et al.* and Sagner *et al.*

As pointed out above, claims 27 and 28 are not anticipated by Hoon *et al.* (U.S. Patent 6,057,105) because Hoon *et al.* teach ***PCR-amplification*** of β-actin (and suitable PCR-primers therefor) along with PCR-amplification of MAGE from cDNA synthesized by unspecific reverse transcription using oligo (dT), while the present invention (US2006/0147928) teaches cDNA-primers hybridizing to at least two different MAGE gene transcripts and to an appropriate calibrator mRNA like that of β-actin, respectively, for simultaneous ***reverse transcription*** of MAGE and calibrator mRNA in a single cDNA-synthesis reaction. Likewise, claims 27 and 28 are not anticipated by Hoon *et al.* because the reference teaches ***PCR-amplification*** of GAPDH (and suitable PCR-primers therefor) along with PCR-amplification of MAGE from cDNA synthesized by unspecific reverse transcription using oligo (dT), while the present invention teaches cDNA-primers hybridizing to at least two different MAGE gene transcripts and to an appropriate calibrator mRNA like that of GAPDH, respectively, for simultaneous ***reverse transcription*** of MAGE and calibrator mRNA in a single cDNA-synthesis reaction.

Likewise, claims 27 and 28 are not anticipated by Kirken *et al.* because the reference (like Hoon *et al.*) relates to ***PCR-primers*** (Table 2, page 11 [0144]) for amplification of MAGE-

A1, 3, 4, 6, 10, 12 and not to ***cDNA-primers*** for reverse transcription as the present invention. Kirken *et al.* teach using at least one primer for simultaneous ***amplification*** of at least two different MAGE templates in a single ***polymerase chain reaction (PCR)***. In contrast, the present invention teaches using at least one cDNA-primer for simultaneous ***reverse transcription*** of at least two different MAGE transcripts in a single ***cDNA-synthesis reaction***. Actually, Kirken *et al.* like Hoon *et al.* teach to carry out cDNA-synthesis by reverse transcription using unspecific priming by oligo(dT) (US2006/0051324, Example I, page 10 [0144], lanes 18-20) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention.

Therefore, these claims, as well as dependent claims 31 and 32, are not rendered obvious by Hoon *et al.* or Kirken *et al.* in further view of Gellerfors *et al.* (U.S. Patent 6,537,777) and Sagner *et al.* (U.S. Patent 6,691,041), both relating to PCR-amplification of PBGD (and suitable PCR-primers therefor), in particular because both teach PCR-primers for PCR-amplification from cDNA obtained through ***unspecific priming*** of poly-A RNA or total RNA by oligo-dT (Gellerfors *et al.*, column 12, lanes 2-8) or through reverse transcription using ***unspecific priming*** by randomized hexamers (Sagner *et al.*, column 12, Example 1, Table). In contrast, the present invention teaches PCR-primers, which are different in sequence from those taught by Gellerfors *et al.* and Sagner *et al.*, for PCR-amplification of PBGD from cDNA obtained through ***specific priming*** by a distinct PBGD cDNA-primer along with specific priming.by at least one MAGE cDNA-primer for simultaneous reverse transcription of at least two different MAGE transcripts in a single cDNA-synthesis reaction (see above).

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

D. Hoon *et al.*/Kirken *et al.* in view of Boon-Falleur *et al.* and Buck *et al.*

As pointed out above, claims 19 is not anticipated by Hoon *et al.* (U.S. Patent 6,057,105) because the refernece relates to ***PCR-primers*** (SEQ ID NO: 1, 2, 23, 24) for amplification and not to ***cDNA-primers*** for reverse transcription as the present invention (US2006/0147928). Hoon *et al.* teach using at least one primer for simultaneous ***amplification*** of at least two different MAGE templates in a single ***polymerase chain reaction (PCR)***. In contrast, the present invention teaches using at least one cDNA-primer for simultaneous ***reverse transcription*** of at least two different MAGE transcripts in a single ***cDNA-synthesis reaction***. Actually, Hoon *et al.* teach to carry out cDNA-synthesis by reverse transcription using unspecific priming by oligo(dT) (U.S. Patent 6,057,105, Example XIII refering to Example X, column 27, lanes 35-38) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention.

Likewise, claim 19 is not anticipated by Kirken *et al.* because the reference (like Hoon *et al.*) relates to ***PCR-primers*** (Table 2, page 11 [0144]) for amplification of MAGE-A1, 3, 4, 6, 10, 12 and not to ***cDNA-primers*** for reverse transcription as the present invention. Kirken *et al.* teach using at least one primer for simultaneous ***amplification*** of at least two different MAGE templates in a single ***polymerase chain reaction (PCR)***. In contrast, the present invention teaches using at least one cDNA-primer for simultaneous ***reverse transcription*** of at least two different MAGE transcripts in a single ***cDNA-synthesis reaction***. Actually, Kirken *et al.* like Hoon *et al.* teach to carry out cDNA-synthesis by reverse transcription using unspecific priming by oligo(dT) (US2006/0051324, Example I, page 10 [0144], lanes 18-20) and not by specific cDNA-primers hybridizing to at least two different MAGE gene transcripts as the present invention.

Therefore, this claim as well as dependent claims 33-34 are not rendered obvious by Hoon *et al.* and/or Kirken *et al.* in further view of Boon-Falleur *et al.* (U.S. Patent 6,221,593) and Buck *et al.* (Biotechniques, Sept. 1999, Vol. 27, No. 3, pp. 528-536), in particular because Boon-Falleur *et al.* teach PCR-primers for PCR-amplification of MAGE-A10 from cDNA obtained through reverse transcription using ***unspecific priming*** (Boon-Falleur *et al.*, column 9, Example 11, lanes 16-20). In contrast, the present invention teaches PCR-primers, which are different in sequence from those taught by Boon-Falleur *et al.*, for PCR-amplification of MAGE-A10 from cDNA obtained through ***specific priming*** by at least one MAGE cDNA-primer (see above). Actually, the MAGE-A10 primers of claims 33-34 were selected among those particularly suited for PCR-amplification from cDNA obtained through ***specific priming*** by at least one MAGE cDNA-primer, for achieving the highest sensitivity for detection of rare tumor cells by the real-time RT-PCR of the present invention (US2006/0147928 Example 10, Tables 10 and 11). This selection could be anticipated neither from U.S. Patent 6,221,593 (Boon-Falleur *et al.*) alone because it relates to unspecific instead of specific cDNA-priming nor in combination with Biotechniques, Sept. 1999, Vol. 27, No. 3, pp. 528-536 (Buck *et al.*) because the latter does not specifically relate to MAGE-A10 primers at all but exclusively deals with sequencing primers in general, whose exchangeability does not apply to primers for other purposes than sequencing like PCR-primers and cDNA-primers as pointed out above.

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited

to contact the undersigned attorney at 512-536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

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